REMARKS

Claims 1, 3-10, and 12-15 are pending. Claims 2, 11, and 16-19 are canceled.

Support for Amendments

The specification is amended for a minor informality. Support for "Doxo" and "doxo" can be found in Examples 1 and 2 as filed.

Claim 1 is amended to incorporate preferred doses for Et 743 and doxorubicin. Support can be found in the specification as originally filed, for example at page 7, 2nd full paragraph, page 8, last paragraph, page 10, Example 1, last paragraph, page 14, Example 2, middle paragraph, and page 15, Table 4. Claim 3 is amended to remove dependency from canceled claim 2, claim 10 is amended to depend from claim 6, and claims 12 and 13 are amended to remove dependency from canceled claim 11.

No new matter is added.

Information Disclosure Statement

The Examiner points to a discrepancy in the Information Disclosure Statements previously filed with regard to two Takahashi cited references. With respect to Takahashi 2001 (see Office Action, page 3, last paragraph), the Takahashi 2001 reference was properly cited and supplied to the USPTO (and considered by the Examiner as reference #1 on one of the submitted pages of listed references). With respect to Takahashi 2002 (see Office Action, page 3, first paragraph), the Takahashi 2002 reference was properly cited, but a duplicate of Takahashi 2001 was inadvertently supplied in its place. Accompanying this response is a supplemental Information Disclosure Statement with a copy of Takahashi 2002, among other references.

Objection to the Specification

The Office Action objects to the specification for the abbreviations Doxo and doxo. Applicants respectfully traverse the objection on the basis that the specification as filed is sufficient. However, in order to advance prosecution, the specification is amended to indicate that the terms "Doxo" or "doxo" are both abbreviations for doxorubicin. Applicants respectfully request withdrawal of the objection.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 3-8, 11, 14, 15, and 19 are rejected under 35 U.S.C. § 102(b) as anticipated by WO 02/36135 (Takahashi) and WO 00/69441 (Bowman). Applicants respectfully traverse. However, in order to advance prosecution, claim 2 is canceled, and the subject matter of claim 2 is incorporated into claim 1.

It is a well-established principle of patent law that to anticipate a claim, the reference must teach every element of the claim (see MPEP 2131.01). In other words, a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The Federal Circuit has held that "[A]nticipation under § 102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on § 103 which takes differences into account." *Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985).

Neither Takahashi nor Bowman discloses administration of doxorubicin wherein the doxorubicin is administered in a dose of about 50 mg/m^2 or about 60 mg/m^2. With respect to

claim 1, the amounts cited in the Office Action (page 6, lines 1-2) are below the lower limits as claimed in claim 1. Therefore, Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/36135 (Takahashi) and WO 00/69441 (Bowman) in view of Dorr (Cancer Chemotherapy Handbook, 1994, pages 395-416). Applicants note that the national phase entry of Takahashi is currently pending before the USPTO as US 10/416,086, and the national phase of Bowman is currently pending before the USPTO as US 09/787,461. The Office Action argues that it would have been obvious to use the dosing schedules for doxorubicin as provided by Dorr in combination with the teachings of Takahashi for the use of Ecteinascidin 743.

Applicants respectfully traverse on the basis that one of ordinary skill in the art would not properly combine Dorr with either Takahashi or Bowman because Dorr teaches amounts of doxorubicin as a single agent rather than in combination with other agents. However, it is known in the art that doxorubicin in combination with other anticancer agents may result in antagonism between the two agents. For example, Hahn et al. (1993, cited in the attached IDS) reports less-than-additive (possibly antagonistic) cytotoxicity for the combination of paclitaxel (Taxol®) with doxorubicin against cell lines of human breast cancer, human lung adenocarcinoma and human ovarian cancer. Each drug when given alone is known to be active against these tumor types, but from the results, Hahn concludes that certain protocols of doxorubicin and paclitaxel "would have a reduced therapeutic index because the normal tissue toxicities might be additive for the combination drug regimen," (page 2711, left column, third full paragraph). In other words, the combination of doxorubicin and paclitaxel results in increased side effects which limit

the therapeutic index of the combination. Therefore, Hahn teaches away from the use of doxorubicin with another anticancer drug at the single-agent dosages such as taught by Dorr due to the possibility of increased side effects (i.e. normal tissue toxicities).

Applicants traverse the finding of obviousness. However, even if, *arguendo*, a prima facie case of obviousness had been made in the Office Action, Applicants have surprisingly found evidence of unexpected results within a sub-range that rebut any case of obviousness that may have been made. As noted by the Federal Circuit, "[t]he law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). In the present case, Applicants have found that the combination of Et 743 in a dose range of about 0.5 to about 0.75 mg/m^2 for ET-743, and doxorubicin in a dose of about 50 mg/m^2 or about 60 mg/m^2 results in antitumor activity without dose-limiting toxicity. See Table 3 on page 13 of the specification as filed, which shows that five patients had confirmed partial response, and 5 patients had long-lasting stable disease after treatment as claimed. Table 4 in the specification as filed provides additional dose-limiting toxicity data. Therefore, Applicants have found a sub-range that rebuts any case of obviousness that may have been made, and respectfully request withdrawal of the rejection.

Provisional Obviousness-Type Double-Patenting

Claims 1-9 and 19 are provisionally rejected for obviousness-type double patenting over claims 1-11 and 19-20 of US 11/577,790.

Claims 1, 3, and 19 are provisionally rejected for obviousness-type double patenting over claims 12, 33, and 34 of US 09/787,461.

Because the rejections are provisional, Applicants respectfully request that the rejections be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejections and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105020. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105020.

Respectfully submitted,
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